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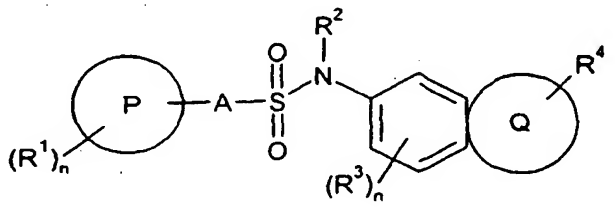
(54) Title: USE OF SULFONAMIDE DERIVATIVES IN THE TREATMENT OF OBESITY OR FOR THE REDUCTION OF FOOD INTAKE



(I)

(57) Abstract: The invention provides a method of treatment or prophylaxis of obesity or for the reduction of food intake, comprising administering to a patient in need of such treatment a therapeutically effective amount of a sulfonamide compound of formula (I). Wherein the substituents are described in the specification.

USE OF SULFONAMIDE DERIVATIVES IN THE TREATMENT OF OBESITY OR FOR THE REDUCTION OF FOOD INTAKE

TECHNICAL FIELD

The present invention relates to the use of sulfonamides and their derivatives, which bind selectively to 5-HT_6 receptors, in the treatment of obesity or for the reduction of food intake.

BACKGROUND ART

Obesity is a condition characterized in an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder in the western world and represents a major health problem in all industrialized countries. This disorder leads to increased mortality due to increased incidences of diseases such as cardiovascular disease, digestive disease, respiratory disease, cancer and NIDDM (type II diabetes). Searching for compounds that reduce body weight has been going on for many decades. One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor subtype profile required is however not known.

Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulate a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin receptor subtypes have been identified and cloned. One of these, the 5-HT_6 receptor, was cloned by several groups in 1993 (Ruat et al. (1993) Biochem. Biophys. Res. Commun., 193: 268-276; Sebben et al. (1994) NeuroReport 5: 2553-2557) This receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT_6 antagonist and 5-HT_6 antisense oligonucleotides to reduce food intake in

rats has been reported (Bentley et al. (1999) Br. J. Pharmac. Suppl 126: P66; Bentley et al. (1997) J. Psychopharmacol. Suppl. A64: 255).

WO01/32646 disclose sulfonamide compounds as ligands selective for the 5-HT_6 receptors, and of proposed value in the treatment or prevention of CNS disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, depression and anxiety. However, it has not been disclosed that such derivatives are useful for the treatment of obesity.

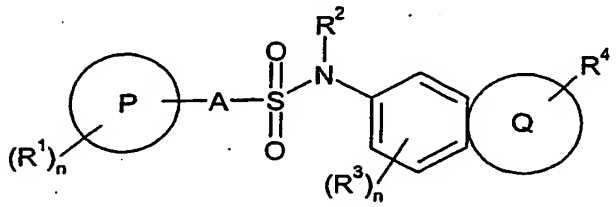
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph depicting the effect on food intake in obese mice by administration of 5-chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid (4-[4-methylpiperazin-1-yl] quinolin-6-yl)amide.

Figure 2 is a graph depicting the effect on food intake in obese mice by administration of 4-*n*-butyl-N-(4-piperazin-1-yl-quinolin-6-yl)benzenesulphonamide.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that 5-HT_6 receptor antagonists, belonging to the class of sulfonamide compounds disclosed in WO01/32646 reduce food intake and body weight. Consequently, the present invention provides a method for the treatment or prophylaxis of obesity in mammals, including humans. The method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a bicyclic or tricyclic heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{2-6}-cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkoxy, C_{1-6}alkoxy- C_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino, or di-C_{1-6}alkylamino;

n is 0, 1, 2, 3, 4 or 5;

R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group $-(CR^6R^7)_p-$ where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;

R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6} alkoxy or together with the group R^2 forms a group $-(CR^6R^7)_p-$ as defined above;

m is 0, 1 or 2;

R^4 is a group $-X-R^5$ where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl; and

R^5 is an optionally substituted 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring comprising 1 to 3 heteroatoms selected from nitrogen, sulfur or oxygen;

Q is a phenyl ring or is a 6 membered heteroaryl ring comprising one or two nitrogen atoms.

In some embodiments of the invention, the body weight disorder to be addressed is obesity in a human, defined as a condition where the individual has a Body Mass Index ("BMI"), sometimes called Quetelet's Index, above currently accepted standards. BMI is calculated by dividing weight (in kg) by height^2 (in meters^2). The current standards for both men and women accepted as "normal" are a BMI of 20-24.9 kg/m^2. Grade I obesity corresponds to a BMI of 25-29.9 kg/m^2 ; Grade II obesity corresponds to a BMI of 30-40 kg/m^2 ; and Grade III obesity corresponds to a BMI greater than 40 kg/m^2. (E. Jequier, "Energy, obesity, and body weight standards," Am. J Clin. Nutr., 45:1035-47 (1987)). Ideal body weight will vary among species and individuals based on height, body build, bone structure, and sex.

The obesity herein may be due to any cause, whether genetic or environmental. Examples of causes that may result in obesity or be the cause of obesity include overeating, diet rich in fats or sugars, environmental causes, medications, pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass. Such induction of body weight increase is particularly suited for treatment using the compounds and compositions resulting from the use or process of the invention, or alternatively the methods of the invention. In this context, "treatment" of a body weight disorder refers e. g., to a reduction of an abnormally or pathologically elevated body weight, or, to a reduction of an abnormally high rate of increase in body weight.

Thus, in one aspect, the invention relates to a method for the inhibition and/or complete suppression of lipogenesis in obese mammals, i.e., the excessive accumulation of lipids in fat cells, which is one of the major features of human and animal obesity, or loss of total body weight, by administration of a compound of any of the formulae herein or a composition including a compound of any of the formulae herein.

Another aspect of the invention is a method for ameliorating the conditions that are a consequence of disease, such as preventing or arresting the progression of polycystic ovarian disease, so that the patient is no longer infertile, and increasing the insulin sensitivity and/or decreasing or eliminating the need or usage of insulin in a diabetic patient, e.g., one with adult-onset diabetes or Type II diabetes, by administration of a compound of any of the formulae herein or a composition including a compound of any of the formulae herein.

Still another aspect of the invention is a method for reducing the food intake in mammals, including humans, by administration of a compound of any of the formulae herein or a composition including a compound of any of the formulae herein.

A further aspect of the invention is a cosmetic use of compounds of formula (I), as described herein, for causing loss of weight, as well as cosmetic compositions containing said compounds.

Yet another aspect of the invention is non-therapeutic method for improving the bodily appearance of a mammal, including a human, in which the method comprises orally administering to said mammal a compound of formula (I) as described herein.

"Treatment" (of obesity) refers to reducing the BMI of the mammal to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or calorie intake by the mammal.

"Prevention" (of obesity) refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The expression "C_{1-6}alkyl" includes methyl and ethyl groups, and straight-chained, branched or cyclic propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "C_{1-6}alkoxy" and "C_{1-6} alkylamino" are to be construed accordingly.

The expression "C_{1-6}alkylene" as used herein refers to straight-chained and branched alkylene groups containing from 1 to 6 carbon atoms. Typical examples include methylene, ethylene, propylene and butylene groups.

The expression "C_{2-6} alkenylene" as used herein refers to straight-chained and branched alkenylene groups containing from 2 to 6 carbon atoms. Typical examples include vinylene, allyl, dimethylallyl and butenylene groups.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having carbon atoms and 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent.

The term "heterocyclic" refers to a nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having carbon atoms and 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent.

When P is naphthyl this is intended to denote both 1-naphthyl and 2-naphthyl groups. When P is a 5 or 6-membered heteroaryl ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. When P is a bicyclic heteroaryl ring suitable examples include indolyl, benzofuryl, benzothienyl, quinolinyl and isoquinolinyl. When P is a tricyclic heteroaryl ring a preferred example is dibenzofuryl. The heteroaryl rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom.

Preferably P is phenyl, naphthyl, benzofuryl or benzothienyl.

Preferably A is a single bond, a methylene or ethylene group or a -CH=CH group. Most preferably A is a single bond.

When n is more than 1 the groups R^1 can be the same or different. Preferably R^1 is halogen (particular chloro or bromo), or a C_{1-6}alkyl group optionally substituted by one or

more halogen atoms, for example, methyl, ethyl, isopropyl, t-butyl or trifluoromethyl.

Preferably n is 0, 1, 2 or 3, particularly 1 or 2.

When R^2 together with a group R^3 forms a further group $-(CR^6R^7)p-$ both of the groups R^6 and R^7 are preferably hydrogen and p is preferably 2.

R^2 is preferably hydrogen.

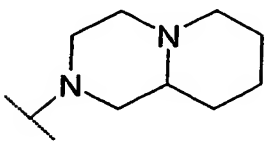
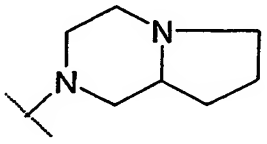
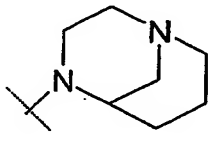
A substituent R^3 can be attached at any unsubstituted carbon atom within the fused ring. When m is more than 1 the groups R^3 can be the same or different. It will be appreciated that when the R^2/R^3 groups are linked together, the group R^3 must be attached to one of the carbon atoms of the fused ring with an ortho relationship with respect to the sulfonamide linkage.

Preferably m is 0.

The group R^4 can be attached at any unsubstituted carbon atom within the ring Q.

When R^5 is a 5- to 7- membered heterocyclic ring suitable examples include piperazinyl, piperidyl, pyrrolidinyl and morpholinyl. The 5- to 7- membered heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom. It will be appreciated however, that when X is O, NH or N-C_{1-6}alkyl then the 5- to 7- membered heterocyclic ring must be linked to the rest of the molecule via a carbon atom. Preferably X is a single bond (i.e. $R^4 = R^5$) and the 5- to 7-membered heterocyclic ring is attached to the rest of the molecule via a suitable nitrogen atom.

When R^5 is a bicyclic heterocyclic ring, X is preferably a single bond (i.e. $R^4 = R^5$) and suitable examples of such groups are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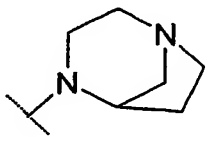


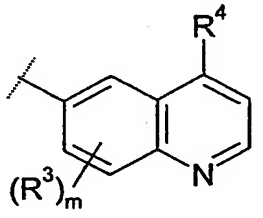
Optional substituents for rings within the definition of R^5, which can be present on

carbon and/or nitrogen atoms, include C_{1-6}alkyl, in particular methyl.

Most preferably R^4 is an unsubstituted piperazine or N-methyl piperazine attached to the rest of the molecule via a suitable nitrogen atom.

Suitably Q is a phenyl ring or is a 6 membered heteroaryl ring comprising one or two nitrogen atoms. Preferably Q, together with the phenyl ring to which it is fused, forms a quinoline, isoquinoline or quinazoline ring.

Most preferably Q, together with the phenyl ring to which it is fused, forms a quinoline ring, and the substituent R^4 is at the 4-position, that is to say, a group of formula (A)



(A)

Particular preferred compounds of this invention include:

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[4-methylpiperazin-1-yl] quinolin-6-yl)amide,

5-chloro-naphthalene-2-sulfonic acid (4-[4-methyl-piperazin-1-yl]-quinolin-6-yl)amide,

4-bromo-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]benzenesulfonamide,

3,5-dichloro-*N*-[4-(4-methyl-piperazin-1-yl)-quinolin-6-yl]benzenesulfonamide,

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(3,5-dimethylpiperazin-1-yl)-quinolin-6-yl]amide,

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(4-methyl-piperazin-1-yl)-quinazolin-6-yl]amide,

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

3,5-dichloro-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,

5-chloro-3-methyl-benzofuran-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5,7-dichloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-naphthalene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-naphthalene-l-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-2-methyl- benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

2-dibenzofuran-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-3,7-dimethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

7-chloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

4,6-dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

5,7-dichloro-2-methyl-benzo[b]thiophene-3-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

biphenyl-4-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

4-*tert*-butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,

5-bromo-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

4-*n*-butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,

4-chloro-2,5-dimethyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,

5-chloro-3-ethyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

5-chloro-3-isopropyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl)amide,

4-iodo-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,

1-(5-chloro-3-methyl-benzo[b]thiophene-2-sulfonyl)-8-(4-methyl- piperazin-1-yl)-2,3-dihydro-1*H*-pyrrolo[2,3-g]quinoline,

5-chloro-naphthalene-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-3-methyl-benzofuran-2-sulfonic acid (2-methyl-4-piperazin-1-yl-quinolin-6-yl)amide,

5-chloro-naphthalene-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin- 6-yl)amide,

5-chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl)amide,

5,7-dichloro-3-methyl-benzo[b]thiophen-2-sulfonic acid (3-methyl-4- piperazin-1-yl-quinolin-

6-yl)amide,
5-chloro-3-methyl-benzofuran-2-sulfonic acid (3-methyl-4-piperazin-1-yl-quinolin-6-yl)amide,
4-*tert*-butyl-*N*- [4-(s-hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-quinolin-6-yl-benzenesulfonamide,
5-chloro-3-methyl-benzo[b]thiophen-2-sulfonic acid [4-(S-hexahydro-pyrrolo[1,2a]pyrazin-2-yl)-quinolin-6-yl]amide,
5-chloro-2-methyl-benzo[b]thlophene-3-sulfonic acid (4-[3,5-dimethylpiperazin-1-yl]quinolin-6-yl)amide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-((S)-3-methyl-piperazin-l-yl)-quinotin-6-yl]amide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-((R)-3-methyl-piperazin-l-yl)-quinolin-6-yl]amide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-((R)-3-isopropyl-piperazine- l-yl)-quinolin-6-yl]amide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [4-(*trans*-2,5-dimethyl-piperazine-1-yl)-quinolin-6-yl]amide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid [8-(4-methyl-piperazin-1-yl) naphthalen-2-yl]amide
or a pharmaceutically acceptable salt thereof.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of formula I include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulfonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compounds of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The compounds of formula I, to be used according to the invention, can be prepared according to the methods described in WO01/32646.

EXAMPLE: Effect of compounds on food intake in ob/ob mice

Animals

Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57B1/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-60 % humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

Compounds

The test compounds are dissolved in solvents suitable for each specific compound such as cyclodextrin, cyclodextrin/methane sulfonic acid, polyethylene glycol/methane sulfonic acid, or saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg $kg^{-1}day^{-1}$ are used. The purity of the test compounds is of analytical grade.

Minipump implantation

The animals are weighed at the start of the study and randomized based on body weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Teeuwes and Yam, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min. It takes about 3 h to reach steady state delivery of the compound.

Food intake measurements

The weights of the food pellets are measured at 5 p.m. and at 8 p.m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weighing is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

Determination of plasma concentration

The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring.

A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Statistical evaluation

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after treatment. The values are expressed as mean±SD and mean±SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the per cent basal values. If statistical significance is reached at the level of $p<0.05$, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

Formulation

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[4-methylpiperazin-1-yl] quinolin-6-yl)amide was weighted in and dissolved to half of its final volume with a stock solution of PEG400 and 1.0% Tween 80. 100 mM Sodium Acetate was added to a final concentration of 10 mM. Purified water was added almost to final volume. The pH of the solution was measured and adjusted with 1M HCl. Qs to calculated weight with purified water. The solution was filtered through a 0.45 µm syringe filter (Millex HV).

Composition:			
Example 1	2.3 mg/ml	6.9 mg/ml	23.0 mg/ml
PEG 400	50% w/v	50% w/v	50% w/v
Tween 80	0.5 %w/v	0.5%w/v	0.5% w/v
Sodium Acetate	10mM	10mM	10mM
Properties:			
pH	5,3	5,2	5,2

EXAMPLE 1

Effect on food intake of 5-chloro-3-methyl-benzo[b]thiophene-2-sulphonic acid (4-[4-methylpiperazin-1-yl] quinolin-6-yl)amide.

Compound	mg/kg/day Nominal	Corrected	Css, tot µM	SEM	n	% of basal level Mean	SEM	P vs. Control	Inhibition (%) Based on basal
Vehicle	0				8	65,7	2,8		
EXAMPLE 1	10	10.4	1,00	0,04	8	62,5	6,4	P<0.7	4,9
EXAMPLE 1	30	32.2	1,62	0,13	6	49,3	8,0	P<0.04	25,0
EXAMPLE 1	100	99.1	1,81	0,15	7	49,9	6,7	P<0.02	24,1
mCCP	10	10.9	0,61	0,04	8	31,2	4,7	P<0.003	52,5

mCPP: m-chlorophenylpiperazine (reference compound)
Css, tot : total plasma exposure of the test compound and mCPP respectively at steady state

5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-[4-methylpiperazin-1-yl] quinolin-6-yl)amide reduces food intake in ob/ob mice by 25% and 24 % at 30 and 100 mg/kg/day respectively, as shown in Figure 1.

EXAMPLE 2

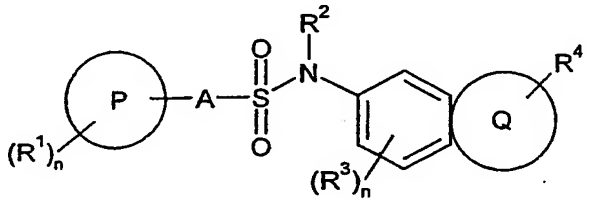
Effect on food intake of 4-*n*-butyl-N-(4-piperazin-1-yl-quinolin-6-yl)benzenesulphonamide.

Compound	mg/kg/day Nominal	Corrected	Css, tot. µM	SEM	n	% of basal level Mean	SEM	P vs. Control	Inhibition (%) Based on basal
Vehicle	0				8	65,2	4,9		
EXAMPLE 2	10	10,9	0,37	0,05	8	61,0	3,0	P<0.40	6,5
EXAMPLE 2	30	36,1	0,94	0,05	8	45,5	4,2	P<0.005	30,2
EXAMPLE 2	100	117,0	1,29	0,09	8	43,6	5,1	P<0.002	33,2
mCCP	10	11,3	0,78	0,03	8	39,4	2,9	P<0.002	39,6

4-*n*-Butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide reduces food intake in ob/ob mice by 30 % and 33 % at 30 and 100 mg/kg/day respectively, as shown in Figure 2.

CLAIMS

1. A method for the treatment and/or prevention of obesity or for the reduction of food intake, comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug thereof, having a structure in accordance with formula (I):



(I)

wherein

P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a bicyclic or tricyclic heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{2-6}-cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkoxy, C_{1-6}alkoxy- C_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino, or di-C_{1-6}alkylamino;

n is 0, 1, 2, 3, 4 or 5;

R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group $-(CR^6R^7)_p-$ where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;

R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6} alkoxy or together with the group R^2 forms a group $-(CR^6R^7)_p-$ as defined above;

m is 0, 1 or 2;

R^4 is a group $-X-R^5$ where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl; and

R^5 is an optionally substituted 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring comprising 1 to 3 heteroatoms selected from nitrogen, sulfur or oxygen;

Q is a phenyl ring or is a 6 membered heteroaryl ring comprising one or two nitrogen atoms.

2. The method according to claim 1 in which said compound is in accordance with said formula (I) wherein P is phenyl, naphthyl, benzofuryl or benzothienyl.

3. The method according to claim 1 or 2 in which said compound is in accordance with said formula (I) wherein R^1 is halogen (particular chloro or bromo), or a C_{1-6}alkyl group optionally substituted by one or more halogen atoms.

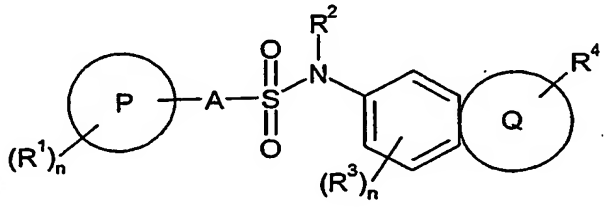
4. The method according to any one of claims 1 to 3 in which said compound is in accordance with said formula (I) wherein R^4 is a piperazine ring optionally substituted by C_{1-6}alkyl.

5. The method according to any one of claims 1 to 4 in which said compound is in accordance with said formula (I) wherein Q together with the phenyl group to which it is fused forms a quinoline, isoquinoline or quinazoline ring.

6. The method to any one of claims 1 to 5 wherein R^4 is a piperazine ring optionally substituted by C_{1-6} alkyl; and Q together with the phenyl group to which it is fused forms a quinoline ring.

7. The method according to any one of claims 1 to 6 in which the compound is selected from:
4-*tert*-butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide,
5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

8. Use of a compound having a structure in accordance with formula (I)



(I)

wherein

P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a bicyclic or tricyclic heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{2-6}-cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkoxy, C_{1-6}alkoxy- C_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino, or di-C_{1-6}alkylamino;

n is 0, 1, 2, 3, 4 or 5;

R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group $-(CR^6R^7)_p-$ where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;

R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6} alkoxy or together with the group R^2 forms a group $-(CR^6R^7)_p-$ as defined above;

m is 0, 1 or 2;

R^4 is a group -X-R^5 where X is a single bond, CH_2, O, NH or N-C_{1-6}alkyl; and

R^5 is an optionally substituted 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring comprising 1 to 3 heteroatoms selected from nitrogen, sulfur or oxygen; and Q is a phenyl ring or is a 6 membered heteroaryl ring comprising one or two nitrogen atoms, in the manufacture of a medicament for the treatment of obesity.

9. The use according to claim 8 in which said compound is in accordance with said formula (I) wherein P is phenyl, naphthyl, benzofuryl or benzothienyl.

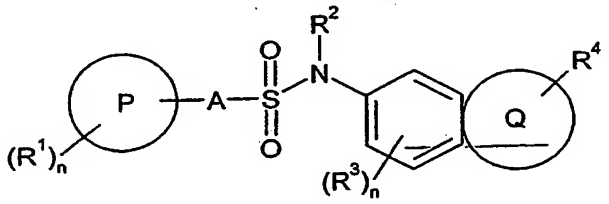
10. The method according to claim 8 or 9 in which said compound is in accordance with said formula (I) wherein R^1 is halogen (particular chloro or bromo), or a C_{1-6}alkyl group optionally substituted by one or more halogen atoms.

11. The use according to any one of claims 8 to 10 in which said compound is in accordance with said formula (I) wherein R^4 is a piperazine ring optionally substituted by C_{1-6}alkyl.

12. The use according to any one of claims 8 to 11 in which said compound is in accordance with said formula (I) wherein Q together with the phenyl group to which it is fused forms a quinoline, isoquinoline or quinazoline ring.

13. The use according to any one of claims 8 to 12 in which the compound is selected from: 4-*tert*-butyl-*N*-(4-piperazin-1-yl-quinolin-6-yl)benzenesulfonamide, 5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-piperazin-1-yl-quinolin-6-yl) amide,

14. Use as a cosmetic product of a compound having a structure in accordance with formula (I):



(I)

wherein

P is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a bicyclic or tricyclic heteroaryl ring comprising 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

A is a single bond, a C_{1-6}alkylene or a C_{2-6}alkenylene group;

R^1 is halogen, C_{1-6}alkyl optionally substituted by one or more halogen atoms, C_{2-6}-cycloalkyl, phenyl, COC_{1-6}alkyl, C_{1-6}alkoxy, OCF_3, hydroxy, hydroxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkoxy, C_{1-6}alkoxy- C_{1-6}alkoxy, nitro, amino, C_{1-6}alkylamino, or di-C_{1-6}alkylamino;

n is 0, 1, 2, 3, 4 or 5;

R^2 is hydrogen, C_{1-6}alkyl or together with a group R^3 forms a group $-(CR^6R^7)_p-$ where R^6 and R^7 are independently hydrogen or C_{1-6}alkyl and p is 2, 3 or 4;

R^3 is C_{1-6}alkyl optionally substituted by one or more halogen atoms, halogen, C_{1-6} alkoxy or together with the group R^2 forms a group $-(CR^6R^7)_p-$ as defined above;

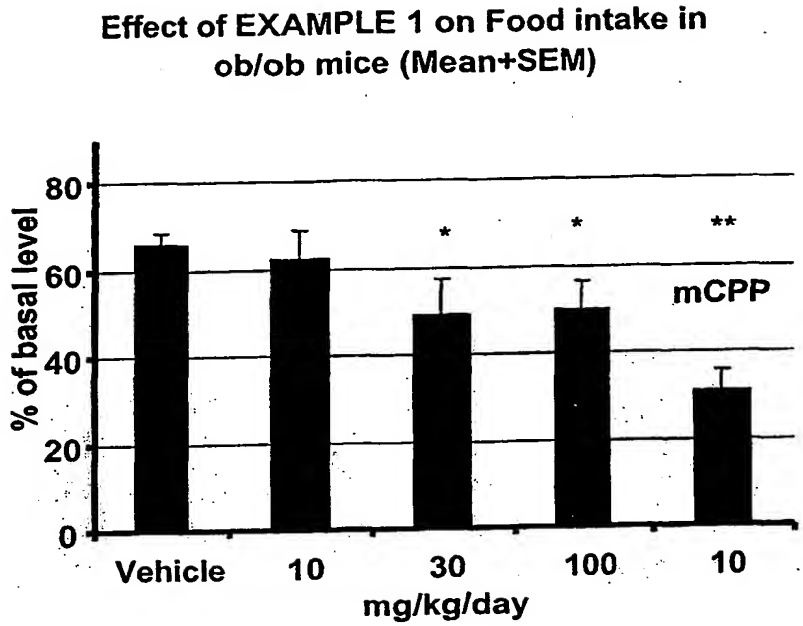
m is 0, 1 or 2;

Q is a phenyl ring or is a 6 membered heteroaryl ring comprising one or two nitrogen atoms.

15. Cosmetic compositions, characterized in that they contain a compound as defined in claim 14.

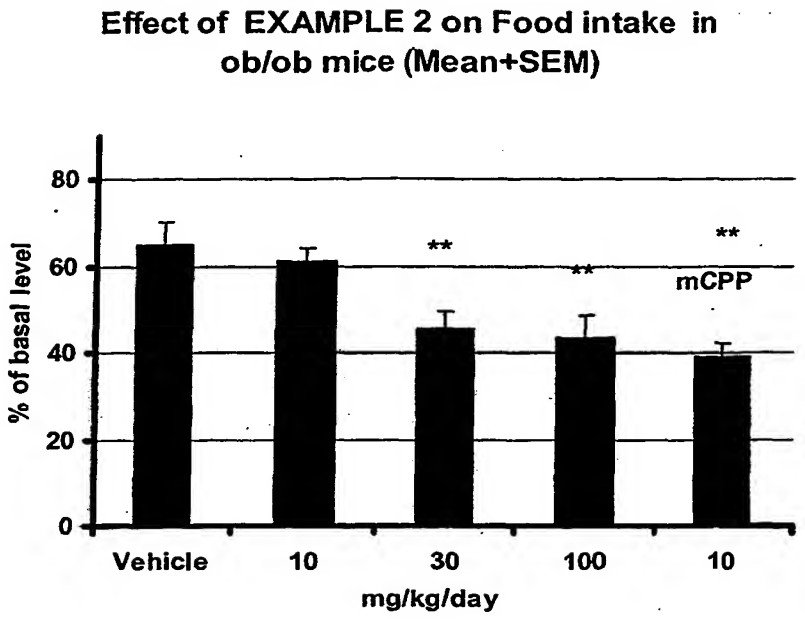
16. A non-therapeutic method of improving the bodily appearance of a mammal, in which the method comprises orally administering to said mammal a compound as defined in claim 14, or a pharmaceutically effective salt thereof, in a dosage effective to reduce appetite, and repeating said dosage until a cosmetically beneficial loss of body weight has occurred.

Figure 1



mCPP: m-chlorophenylpiperazine (reference compound)

Figure 2


Effect of EXAMPLE 2 on Food intake in ob/ob mice (Mean+SEM)
% of basal level
80
60
40
20
0
**
**
**
mCPP
Vehicle
10
30
100
10
mg/kg/day

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02019

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/496, A61P 3/04 // C07D 403/04, C07D 409/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, EMBASE, MEDLINE, BIOSIS, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9421619 A1 (PFIZER INC.), 29 Sept 1994 (29.09.94), see example 18, page 33, and the claims	1-16
X	WO 9944609 A1 (MERCK & CO. INC.), 10 Sept 1999 (10.09.99), see claims	1-16
Y	WO 0132646 A2 (SMITHKLINE BEECHAM P.L.C.), 10 May 2001 (10.05.01)	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2003	07 -02- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer NEBIL GECER/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02019

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	British Journal of Pharmacology, Volume 126, 1999, Suppl., 66P, J.C. Bentley et al: "Effect of the 5-HT6 antagonist, Ro 04-6790 on food consumption in rats trained to a fixed feeding regime" --	1-16
A	Obesity Research, Volume 3, suppl. 4, Nov, 1995, Colin T. Dourish: "Multiple Serotonin Receptors: Opportunities for New Treatment for Obesity", pages 449S-461S --	1-16
A	WO 9827081 A1 (SMITHKLINE BEECHAM PLC.), 25 June 1998 (25.06.98) --	1-16
A	WO 9942465 A2 (SMITHKLINE BEECHAM PLC), 26 August 1999 (26.08.99) --	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/02019

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-7
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/SE02/02019

Claims 1-7 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No. PCT/SE 02/02019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9421619 A1	29/09/94	AT 201403 T	15/06/01
		AU 6391894 A	11/10/94
		CA 2158457 A	29/09/94
		DE 69427289 D,T	06/09/01
		DK 689536 T	30/07/01
		EP 0689536 A,B	03/01/96
		SE 0689536 T3	
		ES 2157256 T	16/08/01
		FI 941213 A	17/09/94
		GR 3036394 T	30/11/01
		HU 67312 A	28/03/95
		HU 9400760 D	00/00/00
		IL 108923 D	00/00/00
		JP 2810236 B	15/10/98
		JP 8503228 T	09/04/96
		PT 689536 T	30/11/01
		US 2001004669 A	21/06/01
		US 2002058811 A	16/05/02
		ZA 9401806 A	15/09/95
WO 9944609 A1	10/09/99	AU 2790999 A	20/09/99
		GB 9812214 D	00/00/00
		US 6043253 A	28/03/00
WO 0132646 A2	10/05/01	AU 1278701 A	14/05/01
		EP 1228066 A	07/08/02
		GB 9926302 D	00/00/00
WO 9827081 A1	25/06/98	AP 9901556 D	00/00/00
		AU 729056 B	25/01/01
		AU 6090498 A	15/07/98
		BG 103530 A	31/01/00
		BR 9713734 A	28/03/00
		CN 1246116 A	01/03/00
		CZ 9902203 A	17/11/99
		EA 2351 B	00/00/00
		EP 0946539 A	06/10/99
		GB 9626377 D	00/00/00
		HU 0000658 A	28/02/01
		IL 130297 D	00/00/00
		JP 2001506646 T	22/05/01
		NO 993003 A	18/06/99
		NZ 335970 A	26/10/01
		PL 334337 A	28/02/00
		SK 80899 A	14/02/00
		TR 9901361 T	00/00/00
		TW 418205 B	00/00/00
		US 6423717 B	23/07/02
		ZA 9711319 A	17/06/99
		AU 711629 B	21/10/99
		AU 2172797 A	29/10/97
		GB 9700901 D	00/00/00
		JP 3204673 B	04/09/01
		JP 2000507705 T	20/06/00
		GB 9722757 D	00/00/00

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/12/02

International application No.
PCT/SE 02/02019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9942465 A2	26/08/99	AU 1047899 A	15/06/99
		CA 2321278 A	26/08/99
		EP 1066288 A	10/01/01
		GB 9803411 D	00/00/00
		JP 2002504484 T	12/02/02